Complete Summary

GUIDELINE TITLE

Assessment: Neurologic risk of immunization. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.

BIBLIOGRAPHIC SOURCE(S)

Fenichel GM. Assessment: Neurologic risk of immunization: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1999 May 12;52(8):1546-52. [30 references] PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Vaccine-associated neurologic disorders

GUIDELINE CATEGORY

Risk Assessment
Technology Assessment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Neurology
Pediatrics

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

- To review the evidence associated with neurologic disorders attributed to vaccine administration

TARGET POPULATION

Infants, children, and adults who may be vaccinated

INTERVENTIONS AND PRACTICES CONSIDERED

Immunization with the following vaccines:

1. Diphtheria and tetanus toxoids vaccine
2. Haemophilus influenzae type B (Hib) vaccine
3. Hepatitis B vaccine
4. Influenza vaccine
5. Measles, mumps, and rubella (MMR) vaccine
6. Whole-cell pertussis vaccine
7. Acellular pertussis vaccine
8. Inactivated poliomyelitis (IPV) and oral poliomyelitis (OPV) vaccines
9. Rabies vaccine
10. Varicella vaccine

MAJOR OUTCOMES CONSIDERED

Adverse neurologic reactions related to vaccines, including:

- Febrile seizures (measles vaccine and pertussis whole-cell vaccine)
- Measles encephalitis (measles vaccine)
- Encephalopathy (pertussis whole-cell vaccine)
- Paralytic poliomyelitis (live attenuated polio vaccine)
- Brachial plexus neuritis (tetanus toxoid vaccine)
- Guillain-Barré syndrome (tetanus toxoid vaccine)
- Acute cerebellitis (varicella vaccine)

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence Concerning Adverse Events Associated With Immunization

Class I. Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II. Evidence provided by one or more well-designed clinical studies such as case–control studies, cohort studies, etc.

Class III. Evidence provided by expert opinion, nonrandomized historical control subjects, or one or more case reports

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

This guideline was reviewed by numerous individuals and the American Academy of Neurology Sections, as well the American Academy of Pediatrics, the Child Neurology Society, the Canadian Infectious Disease Society, and the American Public Health Association.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

Each vaccine assessment includes a rating for the quality of evidence supporting it, as well as a ranking of the causal relationship as assessed by the Institute of Medicine, when applicable. Definitions of the levels of evidence (Class I, Class II and Class III) and the ranking of the causal relationship (1 through 5) are provided at the end of the Major Recommendations field.

Conclusions

Vaccines currently licensed for use in the United States have an excellent safety record, and have greatly reduced the morbidity and mortality caused by infectious diseases in children and adults. All physicians should support the national vaccine initiative.

Recommendations

First, physicians should become better informed about the adverse reactions to modern vaccines and be hesitant to assume a cause-and-effect relationship based on only a temporal relationship.

Also, physicians who observe an adverse event in temporal relationship to vaccine administration are urged to report such incidents to the Vaccine Adverse Event Reporting System (VAERS) (for more information, go to the VAERS Web site).

Summary of Evidence by Vaccine Type

Diphtheria and Tetanus Toxoids

Adverse reactions to diphtheria toxoid in infants cannot be analyzed separately from tetanus toxoid because both are always administered together. No adverse events have been attributed to diphtheria toxoid. Tetanus toxoid is given alone after injury or burn exposure to children and adults. One unique patient developed three episodes of Guillain-Barré syndrome after three doses of tetanus toxoid. The episodes were separated by 9 and 5 years, and the intervals between immunization and onset of symptoms were 3 weeks, 2 weeks, and 9 days. The patient subsequently experienced additional relapses without prior immunization and was diagnosed as having chronic inflammatory demyelinating polyneuropathy. It is not possible to know whether the tetanus toxoid caused or triggered chronic inflammatory demyelinating polyneuropathy in a susceptible individual. A child was reported to the Vaccine Injury Compensation Program who developed two episodes of Guillain-Barré syndrome after tetanus toxoid

administration. Although these are case reports (Class III), the Institute of Medicine considered the association compelling for a cause-and-effect relationship because of the repeated response even though such an association cannot be established by epidemiologic studies (Class II).

Infants are reported who developed brachial neuritis after routine diphtheria, tetanus, and pertussis immunization. In such cases, the tetanus toxoid is implicated strongly even though these are only case reports (Class III). The Institute of Medicine had concluded that a causal relationship exists between tetanus toxoid and brachial neuritis based on repeated reports in adults (Class III). Brachial neuritis does not occur spontaneously during infancy. All affected infants and most adults with brachial neuritis recover rapidly and completely.

Haemophilus influenzae type B (Hib)

A few cases of Guillain-Barré syndrome after Haemophilus influenzae type B immunization have been reported, but the Institute of Medicine concluded that â œthe evidence (Class III) is inadequate to accept or reject a causal relationship between Haemophilus influenzae type B vaccines and of Guillain-Barré syndrome. Haemophilus influenzae type B has been an extremely effective vaccine and has eliminated almost completely the threat of Haemophilus meningitis in the United States.

Hepatitis B

A plasma-derived hepatitis B vaccine was used from 1982 to 1988; the recombinant product was initially used in late 1987 and has replaced the plasma-derived vaccine completely. Post-marketing surveillance for neurologic adverse events after the use of the plasma-derived vaccine showed a few cases of Guillain-Barré syndrome, Bell's palsy, and brachial plexitis. A single case of acute cerebellar ataxia has been reported after the use of the recombinant vaccine. The evidence (Class III) is insufficient to support a cause-and-effect association.

A more recent concern has been a reported association of hepatitis B vaccine and multiple sclerosis in adults but not children. The concern began when in 1991 hepatitis B immunization of health care workers became mandatory in France. Thousands of young and middle-age adults, mainly women, were immunized in a relatively short period of time. One neurologist saw several new cases of multiple sclerosis among such women and his experience was published in the public media (Class III). Epidemiologic evidence for a causal association has never been established. Several groups continue to study the issue. No reports have been published, but the incidence of either new cases of multiple sclerosis or exacerbations in established cases does not appear to be increased in recipients of hepatitis B vaccine.

Influenza

A new influenza vaccine is constituted each year depending on the prevalent viral strains that are expected to appear in the United States the following winter. Annual vaccination against influenza is recommended for everyone, but is especially needed for people with chronic diseases. A small increase in the incidence of Guillain-Barré syndrome (slightly less than 10 patients per million

persons vaccinated) was associated with the 1976 influenza vaccine (A, New Jersey-B, Victoria; (Class II), and an increased risk of one to two per million doses has been identified with the influenza vaccines used in 1992 through 1994. During influenza epidemics from 1972 through 1995, estimated rates of influenza-associated death have ranged from approximately 300 to greater than 1,500 per million persons aged 65 years and older. This age group accounts for more than 90% of all influenza-associated deaths. The potential benefits of influenza vaccination clearly outweigh the possible risks for vaccine-associated Guillain-Barré syndrome.

Neurologists have been hesitant to recommend the use of influenza vaccine in individuals with multiple sclerosis even though febrile illnesses, such as influenza, are known to cause relapse. It was their concern that the vaccine itself might cause relapse. A double-blind, placebo-controlled study of influenza vaccine given to patients with multiple sclerosis has shown that the vaccine does not induce relapse and should be used routinely in individuals with multiple sclerosis (Class I).

Measles, Mumps, Rubella (MMR)

Measles, mumps, and rubella are live-attenuated viral vaccines that are administered to infants as a combined vaccine. A live attenuated measles vaccine has been used in the United States since 1963; by 1982, 97% of all children were fully immunized by school entry against measles. The natural disease was eliminated in most states, and the incidence of measles had fallen from almost 500 per 100,000 in 1950 to 0.5 per 100,000 in 1982. During the same period the total number of annual deaths from measles decreased from 700 to 2, and reported cases of measles encephalitis decreased from 300 to 1. Subacute sclerosing panencephalitis, a chronic form of measles encephalitis, has disappeared concomitantly. During the years 1989 through 1991, a resurgence of measles occurred among nonimmunized and not fully immunized individuals, causing 55,000 cases and 147 deaths. This resurgence serves as a reminder that waning disease is not absent disease.

The currently licensed measles vaccine uses the Edmonston B measles virus attenuated by prolonged passage in chick embryo cell culture. Children who receive live-attenuated measles vaccine may develop an asymptomatic case of measles. Some children develop fever, rash, and conjunctivitis in the second week after immunization (incubation period of at least 5 days). Theoretically, children with vaccine-induced measles could develop any of the known complications of natural infection. Conversely, adverse neurologic events that are not associated with natural measles infection are not caused by immunization. The main neurologic complication of measles immunization is febrile seizures in infants during the second week after immunization. Almost all children recover completely (Class II). However, a small number of cases of measles encephalitis with neurologic sequelae have been reported to the Vaccine Injury Compensation Program. Although a cause-and-effect relationship has not been established, the relationship is biologically plausible (Class III).

The mumps vaccine, prepared in chick embryo cell culture, has eliminated natural mumps infection. No adverse neurologic events are associated with the mumps vaccine used in the United States, but a vaccine used in other countries, prepared

from a different viral strain, has been associated with aseptic meningitis (Class III). Nine reports of sensorineural deafness after immunization with measles, mumps, and rubella have been reported (Class III). Three could be explained. Neurologists have been hesitant to recommend from other causes. The other six were unexplained, and if they were adverse events from measles, mumps, and rubella immunization, the mumps component would have the most biological plausibility.

The present rubella vaccine is prepared from human diploid cells and produces an immune response that parallels the natural infection. The Institute of Medicine concluded that the evidence is insufficient to indicate a causal relationship between the current rubella vaccine and radiculoneuritis and other neuropathies. However, the evidence is suggestive of a causal relationship between rubella vaccine and acute arthritis (Class III). As many as 40% of people receiving the current rubella vaccine may develop transitory arthralgias and paresthesias that begin 7 to 21 days after immunization and last from 1 to 3 days. These symptoms are mild and occur more often in adults than in children. Rubella virus vaccine is safe and effective. Neurologic complications have not been established. It has almost eradicated rubella embryopathy. Furthermore, rubella embryopathy has not occurred in children of women who were immunized inadvertently with rubella vaccine while pregnant.

Pertussis

Whole-cell pertussis vaccine has been used widely since 1947 to protect infants from this serious respiratory illness. Several neurologic disorders, especially seizures and encephalopathy, were attributed to the whole-cell vaccine (Class II). A causal relationship was never established for any complications except febrile seizures, unusual crying, and hypotonic-hyporesponsive episodes. A cause-and-effect relationship between whole-cell pertussis vaccine and infantile spasms has been excluded specifically. The pathophysiology of hypotonic-hyporesponsive episodes is unknown; they are presumed to be syncopal and have no sequelae. The possibility that the whole-cell pertussis vaccine could cause an acute encephalopathy that resulted in a chronic brain damage syndrome was never fully excluded (Class II). No means is available by which a diagnosis of whole-cell pertussis vaccine encephalopathy can be established in an individual case.

An acellular vaccine was first recommended to replace the fourth and fifth doses of the whole-cell vaccine in 1992, and is now recommended for the primary immunizations as well. The vaccines licensed in the United States are combined with diphtheria and tetanus toxoids. Many acellular vaccines contain two or more denatured elements of Bordetella pertussis required for immunity but do not contain endotoxin, the substance responsible for local reactions and fever. The newest pertussis vaccine contains only one pertussis antigen-pertussis toxin. The incidence of unusual crying, hypotonic-hyporesponsive episodes, and seizures is reduced 10-fold using the acellular vaccine compared with the whole-cell vaccine (Class II).

The standard of practice concerning the administration of pertussis vaccine in infants and children with underlying neurologic disorders is stated in the "Red Book," a report of the Infectious Disease Committee of the American Academy of Pediatrics "The decision to give pertussis vaccine to infants and children with

underlying neurologic disorders can be difficult and must be made on an individual basis after careful and continuing considerations of the risks and benefits" (Pertussis. In: Peter G., ed., Red book. 24 ed., Elk Grove [IL], 1997. p. 407-409). It is recommended that immunization with whole-cell and acellular pertussis be deferred in children with progressive neurologic disorders. The concern is that administration of the vaccine "may coincide with or hasten the recognition of inevitable manifestations of the disorder, with resulting confusion about causation." It is also recommended to consider deferring immunization in infants and children who have either a personal history of seizures or known neurologic disorders that predispose to epilepsy. This recommendation is based on data that immunization with whole-cell pertussis increases the risk of seizures in such children. Similar data on acellular vaccines do not exist. Children with chronic brain damage disorders (cerebral palsy, epilepsy, and mental retardation) are often at greater risk from respiratory disorder, and the author of the guideline document has recommended immunization with acellular vaccine.

Poliomyelitis

Inactivated poliomyelitis vaccine (IPV) was the first polio vaccine administered. In 1961, inactivated poliomyelitis vaccine was replaced in the United States by an orally administered live-attenuated viral vaccine (oral poliomyelitis vaccine [OPV]). The change occurred because oral poliomyelitis vaccine is administered more easily, confers humoral and mucosal immunity by infecting the gastrointestinal epithelial cells, and children immunized with oral poliomyelitis vaccine can spread the vaccine virus to nonimmunized persons and provide herd immunity. The disadvantage of oral poliomyelitis vaccine is that it can cause paralytic disease, whereas inactivated poliomyelitis vaccine causes only 2 days of low-grade fever in 5% of recipients. All current cases of paralytic poliomyelitis in the United States are either vaccine-related or occurred in children who were exposed in other countries (Class II). The groups at risk are oral poliomyelitis vaccine recipients, nonimmunized contacts of oral poliomyelitis vaccine recipients, and immunodeficient individuals who were oral poliomyelitis vaccine recipients or contacts. The estimated overall frequency of paralytic disease in normal recipients or contacts is 1 per 2.5 million doses distributed. Approximately 93% of recipient cases and 76% of contact cases occur after the first two immunizations, 87% after the first. The interval between vaccine administration and onset of illness is 11 to 58 days. Healthy individuals tend to have a shorter latency than immunosuppressed individuals.

Ten patients with Guillain-Barré syndrome were reported during an immunization campaign in Finland where more than one million doses of oral poliomyelitis vaccine were administered 24 (Class III). Only five cases occurred within 3 weeks of immunization, and four occurred after 6 weeks. Two of the late cases occurred immediately after a diarrheal illness, suggesting the possibility of Campylobacter jejuni as the causative agent. The authors later reviewed the epidemic and found that the incidence of Guillain-Barré syndrome had increased inexplicably in the months just before the oral poliomyelitis vaccine immunization program, and that the administration of oral poliomyelitis vaccine had not increased the incidence further (Class II). They concluded that the vaccine had not caused Guillain-Barré syndrome.

An enhanced trivalent inactivated poliomyelitis vaccine (eIPV) has become the standard polio vaccine in Western Europe because it is safer than oral poliomyelitis vaccine and provides equivalent protection. The Advisory Committee on Immunization Practices (ACIP) has recommended that the schedule of routine childhood immunizations be changed to encourage the expanded use of enhanced trivalent inactivated poliomyelitis vaccine may cause 2 days of fever but has no neurologic complications. Enhanced trivalent inactivated poliomyelitis vaccine will eventually replace oral poliomyelitis vaccine completely.

Rabies

The current rabies vaccine, prepared from rabies virus grown on human diploid cells (HDCV), has an excellent safety record. Rare cases of atypical Guillain-Barré syndrome are reported after use of this vaccine, and one case of a seizure in temporal relationship to postexposure treatment has occurred (Class III). Although human diploid cell vaccine remains the gold standard, newer vaccines prepared on purified chick embryo cells appear to be equally effective both for pre- and postexposure rabies prophylaxis.

Varicella

A live-attenuated varicella vaccine, first developed in 1974, is now available for routine childhood immunization. Its use is recommended for routine immunization in children. It is safe and effective in normal and immunocompromised children and has been shown to protect children with acute lymphocytic leukemia from natural varicella infection. The vaccine produces a mild case of chicken-pox and may be followed by acute cerebellar ataxia (Class III). As in the cerebellitis following wild chickenpox infection, recovery is complete.

Definitions:

Quality of Evidence Concerning Adverse Events Associated With Immunization:

Class I. Evidence provided by one or more well-designed randomized controlled clinical trials.

Class II. Evidence provided by one or more well-designed clinical studies such as case–control studies, cohort studies, etc.

Class III. Evidence provided by expert opinion, nonrandomized historical control subjects, or one or more case reports

Institute of Medicine Ranking of Causality:

1. There is no evidence bearing on a causal relationship.
2. The evidence is inadequate to accept or reject a causal relationship.
3. The evidence favors rejection of a causal relationship.
4. The evidence favors acceptance of a causal relationship.
5. The evidence establishes a causal relationship.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Support of the national vaccine initiative resulting in greatly reduced morbidity and mortality caused by infectious diseases in children and adults.

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The American Academy of Neurology recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Safety

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Fenichel GM. Assessment: Neurologic risk of immunization: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 1999 May 12;52(8):1546-52. [30 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 May

GUIDELINE DEVELOPER(S)

American Academy of Neurology - Medical Specialty Society

SOURCE(S) OF FUNDING

American Academy of Neurology (AAN)

GUIDELINE COMMITTEE

Therapeutics and Technology Assessment Subcommittee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Subcommittee Members: John Ferguson, MD (Chair); Elliot Mark Frohman, MD, PhD; Robert Goldman, MD; Douglas S. Goodin, MD; Philip B. Gorelick, MD, MPH; Chung Hsu, MD, PhD; Andres Kanner, MD; Ann Marini, MD, PhD; Steven Roach, MD; and Edward Westbrook, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: A list of American Academy of Neurology (AAN) guidelines, along with a link to a Portable Document Format (PDF) file for this guideline, is available at the AAN Web site.

Print copies: Available from the AAN Member Services Center, (800) 879-1960, or from AAN, 1080 Montreal Avenue, St. Paul, MN 55116.

AVAILABILITY OF COMPANION DOCUMENTS

- Practice statement definitions. St. Paul (MN): American Academy of Neurology.
- Practice statement development. St. Paul (MN): American Academy of Neurology.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on November 4, 2001. The information was verified by the guideline developer as of December 20, 2001.

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